DECLARATION BY JUNG JU KIM, Ph.D. UNDER 37 C.F.R. § 1.132

I, Kim, Jung Ju declare as follows:

1. I received my Bachelor of Pharmacy degree in College of Pharmacy from Seoul National University, Seoul, Korea in 1986. I received my MS degree from the Department of Physical Pharmacy at College of Pharmacy from Seoul National University, Seoul, Korea in 1988. I received my PhD degree from the Department of Industrial and Physical Pharmacy from Purdue University, Indianapolis, Indiana, USA in 1999.

2. I have been employed by AMOREPACIFIC R&D center of AMOREPACIFIC Corporation, Yonin-si, Gyeonggi-do, Korea, as a Research Scientist in the Department of Skin Research from 1988 to 1990, a Senior Research Scientist from 1990 to 1995 in the Pharmaceutical Research Institute, a Project leader from 1995 to 1997 in the Department of Drug Delivery System, a Principal Research Scientist, a Manager from 1999 to 2005 in the Department of Drug Delivery System, a Director from 2005 to present in the Pharmaceutical Research Institute & Preclinical Research center. From 1995 to 1999, I had been employed by Purdue University, Indianapolis, Indiana, USA, as a Research Assistant in the Department of Industrial & Physical Pharmacy.

3. I have published in peer-reviewed journals and made presentations at various industrial and academic conferences of Drug Delivery and Pharmaceutics. I have applied for many patents as a major inventor and co-inventor and some of them are granted and others are pending. I am affiliated with the domestic and international society for Drug delivery and Pharmaceutics, Controlled Release Society (CRS), American Association of Pharmaceutical Scientists (AAPS). I have been serving as a reviewer for academic journals such as Journal of Korean Pharmaceutical Sciences.

4. By training and experience, I'm familiar with the design of Transdermal dosage form, oral dosage forms, especially oral controlled and sustained release dosage form. I've made a special study of oral controlled release dosage form to optimize drug efficacy and to reduce side effects. Based on formulation and pharmacokinetic study, several advanced oral controlled-release products were successfully lunched in the market.

5. I understand that the pending claim rejection because there was no evidence of superior improvement against Kikuchi et al.(US 2004/0022848) and Oshlack et al. (US 2002/0102302).

6. To prove superiority of my invention, the following tests were conducted by me and my colleagues at AMOREPACIFIC R&D Center, the assignee of the application.

7. With regard to Kikuchi et al. (US 2004/0022848), to prove the unexpected remarkable effect of the present invention, the following experiment was conducted.

7-1. Test preparations

Table 1.

Ingradient (mg)	Kikuchi Preparation 1	Kikuchi Preparation 2	Example 13 of the present invention
Tramadol hydrochloride	150	150	150
Hydrogenated castor oil	150	150	150
Synthetic aluminum silicate	3.8	3.8	-
Hydroxypropylmethylcellulose	58.4	-	-
Glycerin monostearate	-	58.4	-
Ethylcellulose	-	-	62.2
Talc	10.2	10.2	10.2
Magnesium stearate	7.6	7.6	7.6
Total	380	380	380

7-1-(1) Example 13 of the present invention

Thjs preparation is of the present invention.

It was prepared according to the method described in the specification of the present invention. A mixture of hydrogenated castor oil and tramadol hydrochloride was heated to 75°C and mixed until hydrogenated castor oil softened. This was cooled to normal temperature to form solid mass; the mass was pulverized and screened with 20 mesh, thereby to prepare primary granules.

The primary granules were mixed with ethylcellulose and subjected to secondary wet granulation. Thus prepared granules were dried, mixed with talc and magnesium stearate, compressed to adequate form to prepare tablets.

7-1-(2). Kikuchi Preparations 1 and 2

Two different pharmaceutical preparations according to Kikuchi et al. (US 2004/0022848), were prepared.

Primary granulation of Kikuchi Preparations 1 and 2 was processed according to Kikuchi et al. (paragraph 0061) by using hydrogenated castor oil as a hydrophobic additive (waxy substance), melting it, mixing with synthetic aluminum silicate and

tramadol hydrochloride, and then **spraying** thereby to prepare primary granules.

The examiner said in OA dated July 31, 2007,

"Furthermore, although Kikuchi et al. do not explicitly teach a sustained release preparation, properties are the same when the structure and composition are the same. Here, the instant application and the prior art both disclose a primary granulation product containing a hydrophobic additive which is subject to secondary granulation with a hydrophobic wet granulation material. Thus, burden shifts to application to show unexpected results, by declaration or otherwise."

The examiner points out "paragraph 0065" of Kikuchi et al., with regard to secondary granulation of the obtained granules by wet granulation using a hydrophobic wet granulation material. Kikuchi et al. said in paragraph 0065 as follows:

(A) Secondary granulation may be accomplished by wet fluidized bed granulation, wherein a binder solution such as a solution of hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, or sorbitol is used.

(B) Alternatively, secondary granulation may be accomplished by melting granulation, wherein a low-melting-point substance such as polyethylene glycol or glycerin monostearate is used as a binder.

Therefore, secondary granulation of Kikuchi Preparations 1 was processed by wet granulation with the above primary granules and hydroxypropylmethylcellulose. Secondary granulation of Kikuchi Preparations 2 was processed by mixing glycerin monostearate with the above primary granules, heating the mixture and then granulation.

Thus prepared granules were dried, mixed with magnesium stearate, compressed to adequate form to prepare each tablet.

7-2. Test for effect on surface adhesion

The primary granules of Kikuchi Preparation 2 were prepared by using same amount of same granulating substance with ones of Example 13 of the present invention. However, in case of Example 13, adhesion property of the surface of the primary melt granules was covered through secondary wet granulation, thus adhesion toward punch or die was not observed during tablet process, while the granules prepared in Kikuchi Preparation 2 (US 2004/0022848) exhibited serious adhesion in spite of secondary granulation (melt granulation), resulting in impossibility of tablet preparation.

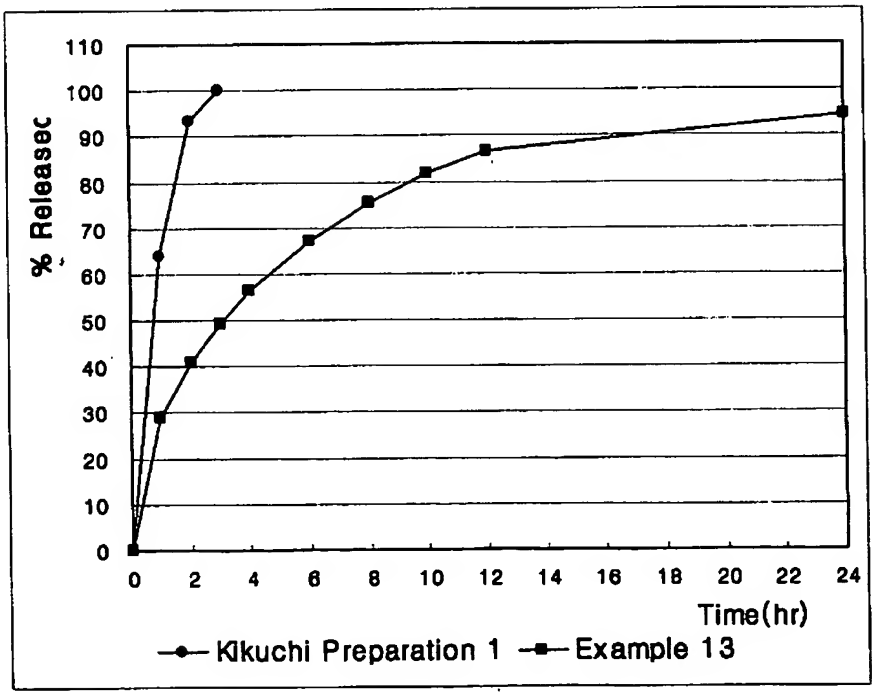
By the way, in case of Kikuchi Preparation 1, the granules were prepared by secondary wet granulation with hydroxypropylmethylcellulose, which is not waxy, but hydrophilic. They were compressed easily into tablet without adhesion, like ones of Example 13 of the present invention.

7-3. Dissolution test

It was possible to prepare the tablet in cases of Example 13 of the present invention and Kikuchi Preparation 1. Release tendency of tablets of the above two preparations was observed by using USP dissolution test device. Time-dependent dissolution rate of drug was determined under the test condition (simulated intestinal solution (Solution II, pH 6.8), paddle type II, 50 rpm/900ml), and result is represented in the following Table 2.

Table 2.

Time (hr)	% Released	
	Kikuchi Preparation 1	Example 13 of the present invention
0	0.00	0.00
1	63.8	28.99
2	93.5	40.90
3	100.1	49.43
4	-	56.33
6	-	67.29
8	-	75.40
10	-	81.68
12	-	86.39
24	-	94.59



Based on the above dissolution test result, it could be confirmed that, in case that tablets were prepared by primary melt granulation with way material and then by secondary wet granulation with hydrophilic material such as hydroxypropylmethylcellulose according to Kikuchi et al. (US 2004/0022848), drug releases rapidly from them, compared to ones prepared by secondary wet granulation with hydrophobic material like Example 13 of the present invention. Especially, in case of freely soluble drug such as tramadol hydrochloride, external water penetrates easily into the internal of tablet due to hydroxypropylmethylcellulose, which is **hydrophilic** secondary wet granulation material. Through the water channel formed, the drug was dissolved rapidly, and then released from the tablet. Furthermore, since the middle of the drug-release, the preparation is disintegrated due to the dissolution of hydroxypropylmethylcellulose itself, and then the primary granules are separated and scattered. Eventually, the increase of the surface area of drug- release is induced and the drug releases very rapidly.

On the other hand, in case of the preparation according to the present invention, external water **cannot penetrate** easily into the internal of tablet due to secondary wet granulation material of **hydrophobic** property. The drug is dissolved slowly from the surface of the preparation, thereby water channels are formed continuously and then the drug can be released through the channels. Therefore, until the drug-release is completion, the whole shape of the preparation is maintained and only the drug is released from the preparation.

It could be confirmed that only the preparation according to the present invention shows the excellent sustained release effect. The present invention was conceived to resolve the problems of the conventional techniques, and its object lies in minimizing the amount of hydrophobic additives for imparting **sustained**-releasing property, and eliminating adhesion phenomenon of granules occurring during the tablet preparation, thereby allowing the production of tablet to be easy (specification [9])

8. With regard to Kikuchi et al. (US 2004/0022848) in view of Oshlack et al. (US 2002/0102302), to prove the unexpected remarkable effect of the present invention, the following experiment was conducted.

8-1. Test preparations

Table 3.

Ingredient (mg)	Preparation K&O	Example 13 of the present invention
Tramadol hydrochloride	150	150
Hydrogenated castor oil	150	150
Ethylcellulose	62.2	62.2
Talc	10.2	10.2
Magnesium stearate	7.6	7.6
Total	380	380

8-1-(1) Example 13 of the present invention

This preparation is Example 13 of the present invention.

It was prepared according to the method described in the specification of the present invention. A mixture of hydrogenated castor oil and tramadol hydrochloride was heated to 75°C and mixed until hydrogenated castor oil softened. This was cooled to normal temperature to form solid mass; the mass was pulverized and screened with 20 mesh, thereby to prepare primary granules.

The primary granules were mixed with ethylcellulose and subjected to secondary wet granulation. Thus prepared granules were dried, mixed with talc and magnesium stearate, compressed to adequate form to prepare tablets.

8-1-(2). Preparation K&O

A mixture of hydrogenated castor oil and tramadol hydrochloride was heated to 75°C and mixed until hydrogenated castor oil softened. This was cooled to normal temperature to form solid mass; the mass was pulverized and screened with 20 mesh, thereby to prepare primary granules.

Secondary granulation was processed by mixing ethylcellulose with the above primary granules, and then heating the mixture thereby to proceed the melt granulation.

8-2. Test for effect on surface adhesion

The primary granules of Preparation K&O were prepared according to the same method by using same amount of same granulating substance with ones of Example 13 of the present invention. However, in case of Example 13, adhesion property of the surface of the primary melt granules was covered through secondary wet granulation, thus adhesion toward punch or die was not observed during tablet process, while the granules prepared in Preparation K&O exhibited serious adhesion.

Preparation K&O shows serious problems in actual production, i.e. reduced flow of particles at hopper, severe adhesion to punch or die at the time of tablet compression and increased resistance at the time of removing tablet from tablet presses,

resulting in impossibility of tablet preparation. During tablet process, the adhesion to punch or die induces irregular hole-formation in the surface of the tablet thereby to induce a large variation of tablet weight and an irregular drug-release. In case of sustained-release preparation, the irregular drug-release can never be accepted because it relates to fatal adverse effect. The adhesion phenomena occur very seriously in the continuous tablet process.

Based on the above test result, it could be confirmed that, although secondary granulation is conducted with hydrophobic material, in case of secondary melt granulation, adhesion property of the surface of the primary melt granules **cannot** be covered through the second granulation. Only in case of secondary wet granulation according to the present invention, adhesion property of the surface of the primary melt granules **can** be covered through second granulation.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like may be punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent issuing from the present application.

Dated: 2008. 1. 4

J. J. Kim

Jung Ju KIM, Ph.D.